Remarks

Claims 1-19 were pending in the subject application. Claims 16-19 are withdrawn from consideration. By this Amendment, claim 1 has been amended, new claim 20 has been added, and claims 16-19 have been canceled. Support for the amendments and new claim can be found throughout the subject specification (*e.g.*, at paragraph 3 of page 14 of the subject specification) and in the claims as originally filed. Entry and consideration of the amendments presented herein is respectfully requested. Accordingly, claims 1-15 and 20 are currently before the Examiner for consideration. Favorable consideration of the pending claims is respectfully requested.

Claims 1-9, 11, 14, and 15 are rejected under 35 USC §103(a) as obvious over Nilsson *et al.* (1997) in view of Nilsson *et al.* (WO 96/09407). In addition, claims 10, 12, and 13 are rejected under 35 USC §103(a) as obvious over Nilsson *et al.* (1997) in view of Nilsson *et al.* (WO 96/09407) and further in view of Sun *et al.* (U.S. published application no. 2004/0161750). Applicant respectfully traverses these grounds of rejection.

Applicant respectfully asserts that the cited references, whether taken alone or in combination, do not teach or suggest the claimed invention. One advantage of the claimed method is that the method can be carried out on a continuous, real-time basis, without the need to obtain samples during the amplification process. Real-time multiplex monitoring of an amplification reaction can therefore be achieved, as outlined in the final paragraph on page 3 of the subject specification. One distinguishing element of the claims, that the amplification of a plurality of different target polynucleotides (*i.e.*, a multiplex reaction) is monitored, in a single chamber, during the amplification reaction, is not taught or suggested by any of the cited references. Applicant respectfully asserts that both the Nilsson *et al.* (1997) and Nilsson *et al.* (WO 96/09407) references teach that nucleic acid amplification products of PCR amplification are detected only after the amplification reaction is complete. The method of the claimed invention wherein the monitoring of the amplification progress is accomplished during the reaction(s) is both surprising and advantageous and is not taught or suggested by any of the cited references.

The Nilsson *et al.* (1997) reference is the primary reference relied upon by the Examiner under both §103 rejections. The Nilsson *et al.* (1997) reference teaches two different strategies for

the scanning and screening of mutations in polymerase chain reaction products by hybridization analysis, with each strategy employing real-time interaction analysis. A first strategy involves the immobilization of PCR products onto the biosensor, while the second strategy involves the immobilization of oligonucleotide primers onto the biosensor. The Examiner recognizes, in paragraph 3 of page 3 of the Office Action, that the Nilsson *et al.* (1997) reference does not teach that the amplification and detection processes are carried out in a single reaction chamber. However, the Examiner considers that combining the Nilsson *et al.* (1997) and Nilsson *et al.* (WO 96/09407) references renders the claimed method obvious. Applicant respectfully asserts that the Nilsson *et al.* (1997) reference teaches away from the claimed invention and that the Nilsson *et al.* (WO 96/09407) reference does not describe the use of a single chamber for both amplification and detection. Therefore, even if the Nilsson *et al.* (1997) and Nilsson *et al.* (WO 96/09407) references are combined, the ordinarily skilled artisan would not arrive at Applicant's claimed method.

As indicated previously herein, the Nilsson *et al.* (1997) reference describes a method of detecting amplified nucleic acids after the amplification reaction is complete. Both of the techniques disclosed by the Nilsson *et al.* (1997) reference involve an initial PCR amplification followed by a physically and temporally separate detection step. In both of the techniques disclosed by the Nilsson *et al.* (1997) reference, the target sequence (P53 gene) is amplified; the PCR amplification products are then immobilized and subjected to two rounds of manipulation, to provide ssDNA for use in the subsequent detection step (see the "single strand preparation" section on page 8 of Nilsson *et al.* (1997)). It is clear that the amplification and detection steps in the Nilsson *et al.* (1997) reference do not take place in the same vessel and there is absolutely no reason why the ordinarily skilled artisan would ignore or modify Nilsson *et al.*'s teaching that manipulation of the PCR amplification products is required between the amplification and detection steps. Applicant respectfully submits that the Examiner has not provided reasoning for her assertion that the use of a single reaction chamber (to perform both amplification and monitoring steps) would be obvious to the ordinarily skilled artisan. As the Examiner is undoubtedly aware, hindsight reconstruction of the prior art to arrive at a claimed invention is not permissible. *In re Sponnoble*, 160 USPQ 237, 243 (CCPA 1969).

Furthermore, when the PCR amplification products are immobilized ("Format 1"), paragraph 1 of column 1 on page 9 of the Nilsson *et al.* (1997) reference teaches that the PCR amplification

products are further purified by ethanol precipitation, prior to immobilization. This provides yet further teaching that the target sequence must be amplified in a first step and then analyzed in a second (and completely different) step. Moreover, the Nilsson *et al.* (1997) reference teaches at column 1 on page 13, that the SPR detection is carried out at a fixed temperature. Clearly, the ordinarily skilled artisan would understand that a PCR reaction cannot be carried out at a fixed temperature; thus, this teaching of the Nilsson *et al.* (1997) reference further reinforces the requirement (and expectation in the art) for separate amplification and detection steps in the method disclosed in the Nilsson *et al.* (1997) reference. It is clear that the Nilsson *et al.* (1997) reference teaches, unambiguously, that amplification and detection steps must be carried out separately. Therefore, the Nilsson *et al.* (1997) reference teaches away from Applicant's claimed invention, which specifies that the detecting step takes place during the amplification reaction, in a single reaction vessel. An invention that contradicts the teachings and express expectations of the prior art has long been accepted as indicia of non-obviousness of an invention. The United States Supreme Court affirmed this principle when it found an invention patentable where the inventor went **against** the accepted teachings, which when taken together, would deter investigation into such a combination. *United States v. Adams*, 383 U.S. 39, 52 (1966).

The Examiner asserts that the combination of the teaching of the Nilsson *et al.* (WO 96/09407) reference with the teaching of the Nilsson *et al.* (1997) reference renders obvious Applicant's claimed method. As indicated above, it is submitted that the Nilsson *et al.* (1997) reference teaches away from Applicant's claimed invention and, thus, there is no objective reason why the skilled artisan would modify the method of the Nilsson *et al.* (1997) reference to arrive at Applicant's claimed method. Furthermore, the Nilsson *et al.* (WO 96/09407) reference does not disclose a multiplex amplification reaction that is monitored during the reaction. The Nilsson *et al.* (WO 96/09407) reference teaches the same general reaction protocol as the Nilsson *et al.* (1997) reference, *i.e.*, the amplification of a polynucleotide in one apparatus and SPR detection of PCR amplification products in a separate apparatus. There is no teaching or suggestion in the Nilsson *et al.* (WO 96/09407) reference of a single apparatus for performing and monitoring a polynucleotide amplification reaction, during the amplification. Therefore, even if the Nilsson *et al.* (1997) and

Nilsson *et al.* (WO 96/09407) references are combined, the ordinarily skilled artisan would not arrive at Applicant's claimed invention.

The Sun *et al.* reference fails to cure the deficiencies of the Nilsson *et al.* (1997) and Nilsson *et al.* (WO 96/09407) references. The Sun *et al.* reference appears to be cited largely due to its disclosure of the use of labelled polynucleotides in the analysis of polynucleotide amplification, using Raman spectroscopy. The Sun *et al.* reference does not teach or suggest a method wherein amplification and detection steps are carried out at the same time in a single reaction chamber. Thus, the Sun *et al.* reference, whether taken alone or in combination with the Nilsson *et al.* (1997) and Nilsson *et al.* (WO 96/09407) references, does not teach or suggest Applicant's claimed invention.

As the Examiner is aware, in order to support a *prima facie* case of obviousness, a person of ordinary skill in the art must generally find both the suggestion of the claimed invention, and a reasonable expectation of success in making that invention, solely in light of the teachings of the prior art and from the general knowledge in the art. *In re Dow Chemical Co.*, 5 USPQ2d 1529, 1531 (Fed. Cir. 1988). One finds neither the suggestion, nor the reasonable expectation of success, of Applicant's claimed invention in the cited references. Thus, Applicant's claimed invention is not obvious over the cited references. Accordingly, reconsideration and withdrawal of the rejections under 35 USC §103(a) is respectfully requested.

In view of the foregoing remarks and amendments to the claims, Applicant believes that the currently pending claims are in condition for allowance, and such action is respectfully requested.

The Commissioner is hereby authorized to charge any fees under 37 CFR §§1.16 or 1.17 as required by this paper to Deposit Account 19-0065.

Applicant invites the Examiner to call the undersigned if clarification is needed on any of this response, or if the Examiner believes a telephonic interview would expedite the prosecution of the subject application to completion.

Respectfully submitted,

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